

AMENDMENTS TO THE CLAIMS

1-5. **(Canceled)**

6. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, which inhibits a kallikrein, of claim 39, wherein the kallikrein is hK2 kallikrein.

7. **(Canceled)**

8. **(Canceled)**

9. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of any one of claims 39, 40, 41, 43, or 47, wherein the serpin sequence is selected from the group consisting of α -1 antichymotrypsin (ACT), protein C inhibitor (PCI), α -1 antiproteinase (AAT), human α -1 antitrypsin-related protein precursor (ATR), α -2-plasmin inhibitor (AAP), human anti-thrombin-III precursor (ATIII), protease inhibitor 10 (PI10), human collagen-binding protein 2 precursor (CBP2), protease inhibitor 7 (PI7), protease inhibitor leuserin 2 (HLS2), human plasma protease C1 inhibitor (C1 INH), monocyte/neutrophil elastase inhibitor (M/NEI), plasminogen activator inhibitor-3 (PAI3), protease inhibitor 4 (PI4), protease inhibitor 5 (PI5), protease inhibitor 12 (PI12), human plasminogen activator inhibitor-1 precursor endothelial (PAI-1), human plasminogen activator inhibitor-2 placental (PAI2), human pigment epithelium-derived factor precursor (PEDF), protease inhibitor 6 (PI6), protease inhibitor 8 (PI8), protease inhibitor 9 (PI9), human squamous cell carcinoma antigen 1 (SCCA-1), human squamous cell carcinoma antigen 2 (SCCA-2), T4-binding globulin (TBG), Megsin, and protease inhibitor 14 (PI14).

10. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, wherein said recombinant inhibitor protein is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 10, and SEQ ID NO: 14.

11-16. **(Canceled)**

17. **(Currently Amended)** A pharmaceutical composition comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, and a pharmaceutically acceptable carrier.

18-27. **(Canceled)**

28. **(Currently amended)** A method for producing the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, comprising

- a) selecting a polynucleotidic sequence encoding a substrate active site modified Reactive Serpin Loop (RSL) which inhibits said Kallikrein;
- b) introducing said polynucleotidic sequence into a sequence encoding a serpin, so as to obtain a recombinant inhibitor protein;
- c) allowing expression of said recombinant inhibitor protein in a cell expression system under suitable conditions; and
- d) recovering said recombinant inhibitor protein.

29. **(Previously Presented)** The method of claim 28, wherein step a) is performed by phage-displayed library screening.

30. **(Previously Presented)** The method of claim 28, wherein the suitable conditions comprise culturing the cell expression system at a temperature between 10-40°C during 10-30 hours.

31. **(Previously Presented)** The method of claim 30, wherein the suitable conditions comprise a temperature of 16°C during 16 hours.

32. **(Currently Amended)** The method of claim 28, wherein step d) is achieved by separation after extraction of said the recombinant inhibitor protein, or inhibiting fragment thereof, from the cell expression system.

33. **(Currently Amended)** The method of claim 32, wherein the separation of said the recombinant inhibitor protein, or inhibiting fragment thereof, is achieved by affinity chromatography.

34. **(Currently Amended)** The method of claim 28, wherein the recombinant inhibitor protein, or inhibiting fragment thereof, is further assayed for its ability to inhibit the activity of said kallikrein.

35. **(Canceled)**

36. **(Previously Presented)** The method of claim 28, wherein the cell expression system is a bacterial cell.

37. **(Canceled)**

38. **(Currently Amended)** A diagnostic kit for the detection of a kallikrein in a specimen comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39.

39. **(Currently Amended)** A recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence with comprising a modified Reactive Serpin Loop (RSL) having amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P'1 scissile bond containing pentapeptide, wherein P1 is an arginine (R) or a lysine (K) which results in increased binding affinity for said kallikrein.

40. **(Currently Amended)** The [[A]] recombinant inhibitor protein, or an inhibiting fragment thereof, of claim 63, wherein the kallikrein is which inhibits kallikrein hK2, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL) having a substituted P1-P'1 scissile bond containing pentapeptide which results in increased binding affinity for said kallikrein hK2.

41. **(Currently Amended)** The [[A]] recombinant inhibitor protein which inhibits a kallikrein, or a kallikrein inhibiting fragment thereof, of claim 39 comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the amino acid substitutions are sequence of the modified RSL is selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22.

42. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 63, wherein the pentapeptide is a substrate peptide selected by said kallikrein using a phage-displayed random pentapeptide library.

43. **(Canceled)**

44-45. **(Canceled)**

46. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 43 39, wherein the at least one additional amino acid substitutions within the P6-P'6 interval are substrate active site sequence is modified in within P3-P'3.

47. **(Currently Amended)** The [[A]] recombinant inhibitor protein, or an inhibiting fragment thereof, of claim 39, wherein the which inhibits a kallikrein, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), modified RSL comprises arginine (R) or lysine (K) at P1, and comprises at least one additional amino acid substitutions within the P6-P'6 interval are modified substrate active site sequence within P5-P'4, which results in increased binding affinity for said kallikrein.

48. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of any one of claims 39, 43, or 47, wherein P'1 is selected from the group consisting of alanine, methionine, proline, leucine, phenylalanine, isoleucine, aspartic acid, and glutamine.

49. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of ~~any one of~~ claims 39, 43, or 47, wherein P'1 is selected from the group consisting of threonine, serine, and valine.

50. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of ~~any one of~~ claims 39, 43, or 47, wherein ~~the additional amino acid substitutions within the P6-P'6 interval are within P3-P'2 of the RSL is modified by at least one substrate active site sequence.~~

51. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[50]] 65, wherein P3-P'2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 56, SEQ ID NO: 58, and SEQ ID NO: 67.

52. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of ~~any one of~~ claims 39, 43, or 47, wherein ~~the additional amino acid substitutions within the P6-P'6 interval are within P4-P'1 of the RSL is modified by at least one substrate active site sequence.~~

53. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[52]] 65, wherein P4-P'1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 35, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 57, SEQ ID NO: 62, SEQ ID NO: 63, and SEQ ID NO: 66.

54. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of ~~any one of~~ claims 39, 43, or 47, wherein ~~the additional amino acid substitutions within the P6-P'6 interval are within P2-P'3 of the RSL is modified by at least one substrate active site sequence.~~

55. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[54]] 65, wherein P2-P'3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 31, SEQ ID NO: 43, SEQ ID NO: 46, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 68.

56. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of any one of claims 39, 43, or 47, wherein the additional amino acid substitutions within the P6-P'6 interval are within P1-P'4 of the RSL is modified by at least one substrate active site sequence.

57. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[56]] 65, wherein P1-P'4 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 34, SEQ ID NO: 38, SEQ ID NO: 48, SEQ ID NO: 54, and SEQ ID NO: 59.

58. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of any one of claims 39, 43, or 47, wherein the additional amino acid substitutions within the P6-P'6 interval are within P5-P1 of the RSL is modified by at least one substrate active site sequence.

59. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[58]] 65, wherein P5-P1 comprises an amino acid sequence set forth in SEQ ID NO: 65.

60. (Canceled)

61. (Canceled)

62. (Currently Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22.

63. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, wherein the amino acid substitutions comprise a substituted pentapeptide sequence spanning the P1-P'1 scissile bond that results in increased binding affinity for said kallikrein.

64. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 63, wherein the substituted pentapeptide sequence is located within the P5-P'4 interval.

65. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 64, wherein the substituted pentapeptide sequence replaces amino acids selected from the group consisting of P5-P1, P4-P'1, P3-P'2, P2-P'3, and P1-P'4.

66. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, wherein the amino acid substitutions are comprised by SEQ ID NO: 39.

67. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, wherein the amino acid substitutions are comprised by SEQ ID NO: 64.

68. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, wherein the amino acid substitutions are modified by at least one additional substrate active site sequence.

69. (New) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 65, wherein the substituted pentapeptide sequences are modified by at least one additional substrate active site sequence.